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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,865	09/28/2000	Erwin Gelfand	2879-68	9468

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/11/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/672,865	GELFAND ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,14,17-19,22-33 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,14,17-19,22-33 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 1/23/03 has been entered and assigned as paper No. 12. Claims 3, 5-13, 15, 16, 20, 21, 34, and 35 have been canceled. Claims 1, 2, 4, 14, 17, 22, 24-28 have been amended, and claims 36-38 are newly added. Claims 1, 2, 4, 14, 17-19, 22-33, and 36-38 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the claim amendment would not be reiterated. The arguments presented in paper No. 12 would be addressed to the extent that they apply to the current rejection.

Claim Objections

Claims 1, 2, 4, and 17-19, 22-28, and 38 stand objected or newly objected to because of the following informalities: the claims encompass more than one invention as defined in Paper #8, upon election of an invention for examination, said claim should be amended to the extent that it reads upon the elected invention. Specifically, the amended claims and new claim 38 read on more than one invention because they recite "an agent", and "said agent", wherein the elected invention is " administration of TNF-alpha". Please note that this is not a species election as explained in paper #8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 14, 17-19, and 22-33 stand rejected, and claims 36-38 are newly rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in paper No. 11 and following.

In paper No. 12, applicants argue regarding the observation in TNF-α transgenic and knock-out mice, that the Examiner has incorrectly contrasted the issue of cellular inflammation in the mice with the development of AHR, and that TNF-α could reduce airway resistance independent of cellular inflammation; applicants submitted new references to indicate that the mouse is a valid model for airway hyper-responsiveness in a mammal, and applicants have previously shown that TNF-α is a potent activator of γδT cells of both mouse and human, thus the outcome of administering TNF-α is predictable. Applicants further argue that the specification provides multiple routes of administration, dose ranges and assays for evaluating the doses, and that the '199 patent reference does not state that systemic administration is not feasible or possible.

The arguments and newly submitted references have been fully considered but found not persuasive for reasons of record advanced in pages 5-9, paper No. 11, and following.

The claims are drawn to a method to reduce airway hyper-responsiveness (AHR) in a mammal by administering tumor necrosis factor-α (TNF-α) to a mammal that has or is at risk of developing a respiratory condition associated with airway hyper-responsiveness (AHR). The specification clearly teaches that "AHR is the result of complex pathophysiological changes in the airway, and a variety of studies have linked

the degree, severity, and timing of the *inflammatory process* with the *AHR"* (Specification, page 2, lines 19-27). Apparently, inflammatory cellular infiltration in the airway tissue is an objective measurement of the recited inflammatory process, is one of the indications of AHR, and contributes to overall airway responsiveness. Accordingly, the statement in the remarks that "TNF-α could reduce airway resistance independent of cellular inflammation" is at least inaccurate, if not contradictory, to what has been taught in the specification because the cellular inflammation itself reflects the state of AHR in the mice.

With regard to the predictability of effects concerning *in vivo* TNF-α administration, previous experiments in γδT cells *in vitro* could not establish the predictability for *in vivo* TNF-α administration because the *in vitro* experiments are simplified compared to an *in vivo* environment, and are limited to how a population of T cells alone responds to TNF-α, whereas the airway tissue comprises many different cell types, not only γδT cells, but also other inflammatory cells, endothelial cells, epithelial cells, and smooth muscle cells, for example. These cells may respond differently to TNF-α, and act in concert to exert an overall effect on airway reactivity. As indicated previously and reiterated here, TNF-α is known to have broad and diverse physiological effects *in vivo*, particularly as an immune modulator and mediator in immune response. As a therapeutic agent, TNF-α has been used in cancer therapies for advanced cases, however, its efficiency has not been proved even though it is backed by solid theoretical bases (*Jones et al*, Prig Growth Factor Rees 1989;1:107-22). With respect to TNF-α in airway hypersensitivity, it is known that decreased γδ T cells in the peripheral blood is

associated with allergic asthmatic individuals (Chen, Clint Exp Allergy 1996;26:295-302, IDS/12), however, multiple cytokines are involved in the regulation of the immune response in addition to TNF-α, (*Yanagihara*, Allergol Intl 1999;48:111-9). Obviously, TNF-α contributes to the regulation of airway hypersensitivity or AHR in a complicated fashion. It is based on the complicity of the biological effects of TNF-α and participation of multiple cell types in controlling the airway responsiveness, the conclusion is drawn that the outcome of administration of TNF-α in an AHR patient is unpredictable.

In fact, the analysis in the previous Office action is supported by several pre- and post-filling publications. For example, *Wheeler et al* (J Appl Physiol. 1990 Jun;68:2542-9) teach that dynamic lung compliance declined and resistance to airflow across the lung increased 30 min after the start of intravenous infusion of TNFα (abstract). *Martin et al* (Am J Physiol Lung Cell Mol Physiol 2001;280:L595-601) teach that in lungs precontracted with methacholine or untreated, administration of TNF-α alone had no effect on airway resistance 10 min after administration; they go on to teach the airway resistance decreases with administration of the combination of TNF- α and IL-1β at 10 min after treatment but started to increase at 40 min after treatment (abstract). *Wagner* (Am J Physiol Heart Circ Physiol 2000 Nov;279:H946-51) teaches that recombinant human TNF-α infused directly into the bronchial airway resulted in a significant decrease on bronchial vascular resistance (BVR) followed by a reversal of tone by 120 min and a sustained increase in BVR to 126% of baseline. *Wagner* concludes, "THUS TNF-α CAUSES BRONCHIAL VASOCONSTRICTION BY THE SECONDARY RELEASE OF ET-1. ALTHOUGH TNF-A EXERTS PRO-INFLAMMATORY ACTIONS ON MOST CELLS OF THE AIRWAYS, VASOACTIVE

PROPERTIES OF THIS CYTOKINE LIKELY FURTHER CONTRIBUTE TO THE INFLAMMATORY STATUS OF THE AIRWAYS" (abstract). In light of these teachings, it is noted that while the specification states, "mice genetically deficient in TNF-α developed AHR and to a greater extent than the C57BL/6 mice" (Specification, page 59, lines 1-2), it does not define the timing and actual measurements beyond cellular inflammation in airway tissue between the two groups; and the specification fails to disclose the occurrence and/or degree of AHR in TNF-α transgenic mice beyond cellular inflammation (which inflammation is similar to controls, and appears to be an indication that AHR is present in these mice). From the parameter of airway tissue cellular inflammation, the specification teaches that the AHR is similar among TNF-α deficient, TNF-α transgenic, and wild type control mice. In view of the foregoing, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

The rejection of claims 30 and 31 is maintained because the parameters recited in the claims do not appear to be enabled in light of the teachings in the cited art.

With regard to the route of administration, the referred teaching of the specification (page 33) generally contemplates administration of any agent, not particular to TNF-α. As previously cited, *Kreig et al* (US 6,429,199) teach, "SOME ACTIVATORS OF DENDRITIC CELLS LIKE LPS OR INFLAMMATORY CYTOKINES (TNF) HAVE DOSE LIMITING TOXICITY, WHICH MAKES THEIR SYSTEMIC USE FOR THIS PURPOSE *NOT PRACTICAL*" (column 25, lines 30-33). Here, "practical" is consistent with the general definition, "concerned with the production or operation of something useful", "Capable of being used or put into effect", which is a synonym of "feasible". Thus, the recitation "not

practical" has the meaning of "not feasible". Further, the newly cited reference (Wheeler et al) indicates that intravenous infusion of TNF-α leads to an effect contrary to what is recited in the preamble of the claim. In view of such, it is maintained that systemic administration does not seem to be enabled for reducing airway hyperresponsiveness in the absence of clarification of the contradictory evidence found in the reference, and such clarification requires factual evidence. The newly submitted claim 37 recites that TNF-α is administered to the lungs of the mammal. However, the specification fails to teach how to deliver TNF-α specifically to the lungs when it is administered systemically.

For reasons of record and those set forth *supra*, the specification fails to meet the statutory requirement set forth under 35 U.S.C. § 112, 1st paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 24, 29-31, 36, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 36, and 38 are vague and indefinite because they are incomplete. The claims provide a method to reduce airway hyperresponsiveness, however, no positive step or recitation clearly relates back to the preamble, which indicates that the goal of the method is resolved.

Claim 24 recites the limitation "said animal". There is insufficient antecedent basis for this limitation in the claim.

Claims 29 and 30 recite the limitation "said step". There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "said step" in lines 1 and 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 14, 17-19, 22, 25, 36, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by *Wheeler et al* (J Appl Physiol 1990;68:2542-9).

Wheeler et al teach a method comprising intravenous administering TNF-α in a pharmaceutically acceptable excipient to the lung of a mammal (e.g. abstract), which administration would activate $\gamma\delta$ T cells in the lung. This is because products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re* Spada, 911 F.2d 705, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Thus, *Wheeler et al* anticipate instant claims.

Please **note** that claim recitation, "to reduce airway hyperresponsiveness" has not given patentable weight in the determination of anticipation for the claimed method because the recitation appears in the preamble as intended use. This is because the intended use of the compound does not constitute a step in the method as claimed. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976); Kropa v. Robie, 88 USPQ 478, 481 (CCPA 1951).

Conclusion

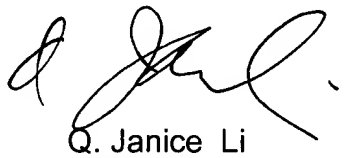
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Examiner
Art Unit 1632

QJL
April 7, 2003